

MICROBIAL PRODUCTION OF NUCLEASE RESISTANT DNA, RNA, AND OLIGO MIXTURES

ABSTRACT

The present method describes the use of thio-phosphate as a feed source for micro-organisms. This compound enters into nucleotide pools and ultimately into polymers of both RNA and DNA forming stable phosphorothioate internucleotide linkages. The method enables the microbial synthesis of both plasmid and phage DNA substituted with phosphorothioate. Furthermore, methods are described for the preparation of phosphorothioate oligo mixtures from recombinant phage DNA grown in modified media for use in antisense studies.

Incorporation of thio-phosphate into the RNA backbone enhances the *in vivo* and *in vitro* stability of such molecules and can be used to significantly increase the amount of mRNA per cell isolated. At reduced concentrations the presence of thio-phosphate in culture media can also be used to significantly enhance the level of protein synthesis in both prokaryotes and eukaryotes. Significant increases in both recombinant and native proteins are made possible with this method.